Mathematical difficulties and white matter abnormalities in subacute pediatric mild traumatic brain injury

Leen Van Beek[a], Pol Ghesquière[a], Lieven Lagae[b] & Bert De Smedt[a*]

[a] Parenting and Special Education, Faculty of Psychology and Educational Sciences, University of Leuven, Belgium
[b] Department of Development and Regeneration, Biomedical sciences group, University of Leuven, Belgium

Author note

Leen Van Beek, MSc
Parenting and Special Education Research Unit
Leopold Vanderkelenstraat 32 – box 3765, B-3000 Leuven, BELGIUM
Phone : +32 16 37 30 97, Email : Leen.VanBeek@ppw.kuleuven.be
Pol Ghesquière, PhD
Parenting and Special Education Research Unit
Leopold Vanderkelenstraat 32 – box 3765, B-3000 Leuven, BELGIUM
Phone: +32 16 32 62 34, Email: Pol.Ghesquiere@ppw.kuleuven.be
Lieven Lagae, MD, PhD
UZ Leuven, Paediatric Neurology
Herestraat 49 - box 7003 20, B- 3000 Leuven, BELGIUM
Phone: +32 16 34 38 45, Email: Lieven.Lagae@uzleuven.be
Bert De Smedt, PhD
Parenting and Special Education Research Unit
Leopold Vanderkelenstraat 32 – box 3765, B-3000 Leuven, BELGIUM
Phone: + 32 16 32 57 05, Email: Bert.DeSmedt@ppw.kuleuven.be

* Correspondence concerning this article should be addressed to Bert De Smedt.

Running title: Mathematical difficulties in pediatric mTBI

Table of contents title: Mathematical difficulties and white matter abnormalities in pediatric mTBI

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Abstract

Mathematical difficulties have been documented following pediatric mild traumatic brain injury (mTBI), yet a precise characterization of these impairments and their neural correlates is currently unavailable. We aimed to characterize these impairments by comparing behavioral and neuroimaging (i.e. diffusion tensor imaging or DTI) outcomes from children with subacute mTBI to typically developing controls. Twenty subacute pediatric mTBI patients and 20 well-matched controls underwent cognitive assessment and DTI examination. DTI tractography was used to detect white matter abnormalities in the corpus callosum (CC) and superior and inferior longitudinal fasciculi; these tracts are involved in mathematical performance and they are often damaged after mTBI. Behavioral results revealed that children with mTBI performed significantly more poorly on rapid apprehension of small numbers of objects (or ‘subitizing’), processing of non-symbolic numerosities and procedural problem solving. These group differences were explained by differences in visuospatial working memory, which suggests that the observed mathematical difficulties may be a consequence of impairments in visuospatial abilities. DTI analysis revealed subtle group differences in the CC genu and splenium, i.e. higher fractional anisotropy and lower mean and radial diffusivity in children with mTBI, but the observed white matter abnormalities of the CC were not significantly associated with the observed mathematical difficulties in the mTBI patients.

Introduction

Traumatic brain injury (TBI) is a major cause of interruption of normal development in childhood and results in significant impairments and functional disabilities, such as cognitive, academic, physical and psychosocial impairments. Pediatric mTBI has recently emerged as an important public health concern. Although children with severe TBI are at high risk for impairments in cognitive functioning and academic skills, children with mild and moderate brain injuries also show elevated behavioral and academic problems compared with children without brain insult.[1-4] Investigating these academic sequelae of TBI is particularly relevant because doing well with schoolwork is one of the major concerns of children and their parents after an injury.[5]

Longitudinal[2, 6, 7] and cross-sectional[1, 8, 9] studies suggest that mathematics rather than reading or spelling is the most compromised in children with TBI. More specifically, poorer arithmetical performance has been reported in children with TBI at the acute[2, 6, 7] and at the chronic[1, 2, 6-9] stage of injury, whereas reading and spelling appear to be relatively spared. Even mTBI patients scored below averaged range on arithmetic tests.[1, 7] It should be noted that the majority of studies on mathematics in TBI has been conducted in children with moderate-to-severe TBI[6] or TBI populations with a variety of severity including mild injuries[1, 2, 7, 9] and this mainly at chronic stages.[1, 8, 9] A precise characterization of the mathematical difficulties in children with mTBI at the subacute stage of injury is currently unavailable. It also remains unclear how these difficulties are related to brain damage, such as white matter abnormalities. Research into these mathematical difficulties is highly needed because numerical skills are crucial to life success in modern societies: our daily life is permeated by numbers, mathematics represents an important part of the curriculum at school, and numerical skills predict later income, employment, mortgage default rates and access to medical services.[10, 11] The present study therefore aimed to characterize the mathematical difficulties in subacute pediatric mTBI at behavioral, cognitive and neural level.

An important drawback of the existing studies on mathematics achievement in children with TBI is that they all examined mathematical performance exclusively with general achievement tests.[1, 2, 7, 9]

Although these data are a crucial first step in examining mathematical difficulties in TBI, general mathematics achievement tests only yield a total score, which reflects performance averaged across all assessed areas of mathematics. However, behavioral studies suggested that mathematics is not a unitary skill, but a multicomponent skill consisting of different subskills, that might be differentially impaired.[12] Thus, one general achievement score does not provide information on the various subcomponents of mathematical performance (e.g., magnitude representation, calculation, problem solving) and does not inform researchers or clinicians about the strengths and weaknesses of children in the broad domain of mathematics. The use of experimental cognitive measures that examine specific mathematical abilities[13] is needed to further shed light on the mathematical difficulties in children with TBI. This approach has been successful in other specific populations that show mathematical difficulties, such as genetic disorders or preterm birth.[14, 15] We focus on three areas of elementary mathematics that have been extensively investigated at behavioral and neural levels in typically developing children and in children with mathematical difficulties without TBI: numerical magnitude processing, enumeration and arithmetic.[16] Measures of numerical magnitude processing and enumeration are unique predictors of later individual differences in mathematical achievement,[16-18] but they have never been studied in children with TBI.

Difficulties in mathematics achievement have been related to impairments in working memory.[19] Deficits in working memory are a common finding in pediatric TBI.[20-25] Even subtle working memory deficits have been observed following mTBI,[24, 26, 27] although most previous studies focused on chronic stages after injury, i.e. several months to years after the accident. Working memory performance shortly after mTBI has rarely been studied. To the best of our knowledge, only Loher and colleagues[28] studied working memory after pediatric mTBI in the first weeks after injury. The authors observed subtle working memory deficits 6 weeks post-injury. Little is also known about the association between working memory and mathematical skills in children with TBI. Only Ewing-Cobbs and colleagues[2] investigated this association and these authors found that mathematics in pediatric TBI were predicted by visuospatial skill and visual memory, but not by verbal working memory. However, these authors only investigated whether general mathematical competence and not different mathematical subskills, were related to working memory in children with varying injury severity including mild injuries. It remains unclear whether such association can be observed in mTBI only. The present study therefore aimed to further elucidate the relationship between working memory and mathematics in mTBI by investigating the relationship between different working memory measures and different mathematical subskills following mTBI.

Although the exact origin of the mTBI-related deficits in cognitive and behavioral functioning is not known, they may be the consequence of diffuse axonal injury (DAI). Diffusion tensor imaging (DTI) has been demonstrated to be sensitive to detect DAI.[29-36] Consequently, DTI has become a promising tool to investigate the functional outcome after pediatric TBI.[37-40] DTI is a MR technique which is sensitive to diffusion of water molecules in the brain[41-44] and has been used to identify and quantify white matter connections. DTI provides different quantitative markers, such as fractional anisotropy (FA), mean diffusivity (MD), axial (AD) and radial (RD) diffusivity, which are determined by both microscopic factors, such as myelination[45] and macroscopic factors, such as crossing fibers. Specifically, FA measures the degree to which diffusion is anisotropic, which depends on the size, density, and organization of the axons, as well as the degree of myelination and number of neural branches per imaging voxel.[42] In fact, FA is highly sensitive to microstructural changes, but it is less specific to the type of change. MD measures the mean diffusion of water but not its directionality.[46] Recently AD and RD have been proposed to yield more specific insights into the pathophysiology of mTBI. AD measures water diffusion parallel to the direction of axons and may reflect axonal properties such as fiber packing density,[47, 48] while RD measures water diffusion perpendicular to the direction of axons and likely corresponds to myelin sheath function.[47-51] It is important to note that while analyses of AD and RD can add valuable information, we have to be extremely careful for conclusions on underlying neuropathology based on differences in these diffusion measures. Indeed, due to the large voxel size, DTI markers do not relate directly to features of tissue microstructure and are sensitive to a variety of micro- and macroscopic factors simultaneously.[50-55]

DTI tractography offers the unique possibility to reconstruct 3D pathways of specific white matter tracts non-invasively and in vivo. This technique can be used to delineate specific tracts of interest and subsequently average quantitative DTI measures can be extracted, compared between groups and correlated with behavioral measures. This approach has been successful in several fields, such as reading[56] and working memory.[57]

The majority of pediatric DTI studies has investigated children with moderate-to-severe TBI[40, 58-62] or TBI populations with a variety of severity including mild injuries[25, 39, 63, 64] at chronic stages. Overall, these studies found decreases in FA and increases in MD, a pattern that is also seen in adult mTBI studies at chronic injury times.[31, 35, 65-69] Findings at (sub)acute stages are less clear-cut. Several adult studies also found a decrease in FA and increase in MD.[29, 30, 66, 70-72] On the other hand, an increase in FA and decrease in MD have been found in adult mTBI patients during (sub)acute time periods.[73-77] Few DTI studies have examined children and adolescents with mTBI during the subacute injury phase: most of these studies reported increased FA and reduced MD/RD [38, 78-80] although others have not found group differences in DTI scalars.[81] As mentioned above, DTI metrics, which are macroscopic measures of diffusion, are influenced by a variety of microscopic (e.g., changes in the concentrations of intra and extracellular water, changes in myelin structure) and macroscopic factors (e.g., crossing fibers) which makes the interpretation of group differences in DTI metrics in light of the underlying microscopic pathology particularly challenging.[55, 75] However, it should be noted that subtle cytotoxic edema and localized inflammation that occur early in the course of injury provide the most plausible explanation of increased FA and reduced MD/RD observed in previous studies.[38, 73, 76, 79] More specifically, mechanical forces of mTBI may stretch the axons and related supporting structures.[82, 83] This might alter the function of gated ion channels resulting in increased intracellular and decreased extracellular water.[84] The decrease in extracellular water may be reflected as a decrease in diffusivity perpendicular to the axon (RD) and hence the overall diffusion (MD). At the same time, the accumulation of intracellular water causes more tightly compacted axons and restricted interstitial space, resulting in an increase in anisotropic diffusion and therefore the fractional anisotropy.[84, 85]

White matter integrity is crucial for higher cognitive functions, such as mathematics. Accordingly, white matter abnormalities after TBI may explain mathematical difficulties in TBI. DTI studies on mathematics are still limited, but suggest that individual differences in mathematics achievement are associated with commissural fibers of the corpus callosum (CC) and long association white matter pathways within fronto-temporo-parietal regions such as the superior (SLF) and inferior longitudinal fasciculi (ILF).[86-96] This is of particular interest because these white matter pathways overlap with the white matter tracts that are often damaged after mTBI. Specifically, Niogi and Mukherjee[97] concluded in their review of DTI studies in mTBI that the CC and long coursing fasciculi, such as the SLF and ILF, are the most commonly damaged tracts. Furthermore, it seems that persistent cognitive problems after injury (e.g., deficits in attention, working memory or processing speed) may be primarily a consequence of DAI in the CC and these long association pathways. Against this background, damage to these white matter pathways could explain the mathematical difficulties in children with mTBI.

The present study aimed to extend the current understanding of mathematical difficulties in children with mTBI at the subacute stage, i.e. within 4 weeks after the injury. In particular, this study wanted to investigate the impact of pediatric mTBI on mathematical skills by using experimental cognitive measures that examine specific mathematical abilities. Against the background of DTI studies which showed that the CC, SLF and ILF are often damaged after mTBI and are also involved in mathematics, we further aimed to verify whether these overlapping white matter tracts are damaged in children with mTBI by using DTI tractography. Finally, we wanted to investigate whether white matter abnormalities in children with mTBI at the subacute stage of injury were related to their difficulties in mathematics.

Materials and methods

Participants

Twenty subacute pediatric mTBI patients (13 boys; 17 right-handed) with ages ranging from 7 to 13 years ($M = 10.80$; $SD = 1.58$) participated in the study. Diagnosis of mTBI was based on the diagnostic criteria of the American Congress of Rehabilitation Medicine[98] and World Health Organization.[99] More specifically, all patients with mTBI had a pediatric Glasgow Coma Scale (GCS) of 13-15, and at least one of the following symptoms: (1) an alteration in mental status at the time of injury (e.g., confusion, disorientation, dizziness); (2) loss of consciousness < 30 minutes, (3) post-traumatic amnesia < 24 hours; and/or (4) other neurological abnormalities that may or may not be transient (e.g., seizure or focal signs). Recruitment occurred through the emergency and pediatrics departments of the University Hospital and Heilig Hart Hospital in Leuven, Belgium. All patients were behaviorally tested and scanned within a time window of maximum 4 weeks after injury. The examinations were performed during two sessions, i.e. first session at home and a subsequent session at the hospital. See Table 1 for a summary of demographic and injury characteristics of the mTBI group.

The control group consisted of 20 well-matched typically developing children (13 boys; 18 right-handed) with ages ranging from 8 to 13 years ($M = 10.88$; $SD = 1.46$). This healthy control group, which was matched in terms of age, sex, verbal-ability, handedness and premorbid mathematical abilities, was recruited from local schools after enrollment of the mTBI patients. An identical series of examinations was performed on this control group.

All participants were native Dutch speakers and had normal or corrected-to-normal vision. They all had normal intelligence (IQ $\geq$ 85) as determined by an abbreviated version of the Dutch Wechsler Intelligence Scale for Children, Third Edition (WISC-III-NL).[100] Handedness was assessed by the Edinburgh Handedness Inventory.[101] mTBI patients and controls were excluded if there was a history of previous TBI, neurologic problems, psychiatric disorders or diagnosis of learning difficulties.

The study was approved by the local Ethical Board and written informed consent according to the Declaration of Helsinki was obtained from the parent of each child and children over age 8; assent was given by each participating child.

Behavioral measures

Mathematical ability

Premorbid mathematical abilities. Premorbid mathematical ability was assessed with a curriculum-based standardized achievement test for mathematics[102] that measured multi-digit calculation, word problem solving and geometry. This test is generally administered in most schools in Flanders, Belgium. The percentile scores were available from assessments completed at school for 35 of the 40 participants (16 mTBI patients, 19 controls) and dated from one month to one year before testing.

Numerical magnitude processing. The representation of numerical magnitudes was assessed with a classic symbolic and non-symbolic magnitude comparison task[103] presented using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA). In each trial two digits or two dot arrays were presented simultaneously. The dot arrays, generated with the MatLab script of Piazza and colleagues,[104] were controlled for non-numerical parameters (i.e., individual dot size and total occupied area). Participants were instructed to respond by pressing the button corresponding to the side of the larger stimulus. Children were instructed to perform both accurately and quickly. There were two blocks of 128 stimuli separated by rest periods. The first block was non-symbolic and the second was symbolic. Each trial consisted of (1) a random inter-stimulus interval for 1250 – 1500 ms, (2), a fixation cross in the center of the computer screen which remained visible for 500 ms, and (3) the stimulus remained until response or for maximum 2500 ms. Practice trials preceded the experiment in order to ensure good understanding of the task. Mean accuracy scores and mean reaction times were used in the analyses.

Enumeration. In this task, children had to enumerate series of dots that varied in number between 2 and 8. Children had to respond by speaking into a voice-key, as quickly as possible, the number of dots that were presented. For each numerosity there were two different stimuli (where the requisite number of targets was placed randomly within an invisible 8 x 8 grid). The task comprised 28 trials (4 for each numerosity). In enumeration tasks it is typically observed that participants are able to enumerate fast and very accurate up to four objects,[105] a process that is called subitizing. When people must enumerate 5 or more objects, they use counting.[105] The mean accuracy and mean reaction time of the subitizing range (2, 3 and 4 dots) as well as the counting range (6, 7 and 8 dots) were used in the analyses.

Arithmetic. Arithmetic was investigated with a single-digit addition task. Single-digit addition problems in the form $a + b$ were used as stimuli. The problems were selected from all possible pairwise combinations of the digits between 2 and 9, with the exclusion of tie problems (e.g., 4 + 4) and problems containing a 0 or 1 as operand or answer. This set comprises 56 problems. From this set 20 small (sums ≤ 10) and 20 large (sums > 10) problems were selected. Arithmetic problems were presented on the screen and the participant was instructed to solve the problem and to speak the solution into a voice-key. Each trial consisted of (1) a fixation cross in the center of the screen, which remained visible for 500 ms, (2) the addition problem, which was shown until response or for maximum 10000 ms, and (3) a fixed inter-stimulus interval of 1500 ms. The child performed 20 practice trials to ensure good understanding of the task. Afterwards, all participants were tested on 80 trials, which were organized in two runs of 40 trials separated by a rest period. A short break was given after 20 trials. Mean accuracy and mean reaction time for small problems as well as for large problems were used in the analyses.

Cognitive measures

Intellectual ability. Children were assessed with an abbreviated version of the Dutch Wechsler Intelligence Scale for Children, Third Edition (WISC-III-NL).[100] The Vocabulary and Block Design subtests were administered and the scores on these subtests were combined into a full scale IQ.[106]

Working memory. Visuospatial and verbal working memory were assessed by four different tasks that are commonly used in research that investigates the association between working memory and mathematical performance in children.[107, 108] These tasks are part of the Working Memory Test Battery for Children.[109] Visuospatial working memory was measured using forward and backward Block Recall, while verbal working memory was measured using forward and backward Digit Recall. Each working memory tasks involves the repetition of sequences of test items. In the forward tasks children are asked to recall items in the same order as presented, while in the backward tasks children had to produce the items in the reverse order as presented. In the Digit Recall tasks sequences of random digits were presented verbally and the child had to verbally repeat them in either the same or reverse order. In the Block Recall task the researcher tapped a sequence of blocks and the child was asked to tap the same blocks in either the same or reverse order. For each task blocks of three trials of a particular sequence length were used. Testing continued until two incorrect responses are given in a block. The score of each working memory task was based on the total number of correct trials that could be recalled by the child. The sum of scores on Block Recall tests and sum of scores on Digit Recall tasks were used in the analyses.

Motor speed. An experimental motor reaction time task presented using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA) was included as a control for children's response speed. Two figures appeared on the screen. One of them was coloured white and the child had to press as soon as possible on the side of this white figure. Twenty experimental trials were preceded by 3 training trials. Mean reaction time was used in the analyses.

DTI tractography

All participants underwent MRI examination on a 3T system (Philips Achieva, Best, The Netherlands). The DTI data were acquired using a single spin shot EPI with SENSE acquisition. DTI images covering the entire brain and brainstem were acquired with the following parameters: 68 contiguous sagittal slices, slice thickness = 2.2 mm, voxel size = $1.96 \times 1.96 \times 2.2$ mm^3, repetition time (TR) = 11043 ms, echo time (TE) = 55 ms, field-of-view (FOV) = 220×220 mm^2, matrix size = 112×109 and acquisition time = 10 min 34 s. Diffusion gradients were applied along 45 noncollinear directions (b = 800 s/mm^2) and one nondiffusion-weighted image was acquired.

Raw diffusion MR data were transferred to an offline workstation. All images were first visually checked for possible artifacts and participants whose images were of poor quality were removed ($n = 2$). Further preprocessing was done using *ExploreDTI*.[110] The preprocessing involved (1) correcting for eddy current distortion and subject motion; (2) diffusion tensor estimation using a non-linear least square method, and (3) whole brain tractography for each DTI data set using a uniform 2 mm seed point resolution, FA threshold of .2 to seed and end tracking, angle threshold of 40°, and fiber length range of 50-500 mm.

Tractography was done with the TrackVis software.[111] We delineated the tracts of interest in native space in order to avoid artifacts due to normalization. As mentioned in the introduction, the genu and splenium of the CC, SLF and ILF were reconstructed due to their involvement in both mTBI and mathematical performance. To reconstruct these tracts, we defined the ROIs according to available validated protocols for delineation of these tracts.[112-114] The SLF and ILF were delineated both in the left and right hemispheres. For each of the tracts the mean FA, MD, AD and RD values were extracted for every subject. To assess the reproducibility of the tractography, the delineation was performed by two independent and experienced raters. We observed high inter-rater reliability as indicated by a DTI parameter intra-class correlation coefficients above .90. Against this background, the average FA, MD, AD and RD across the two raters were used in all subsequent analyses.

Statistical analysis

Statistical analyses were carried out using SPSS version 22 (IBM SPSS Statistics, IBM Corp, New York, USA). Univariate F-tests, controlling for age and sex, were used to assess the effect of group (mTBI patients, controls) at an alpha level of .05 on the behavioral measures (working memory, enumeration, numerical magnitude representation and arithmetic) and DTI measures (mean FA, MD, AD and RD values of the delineated tracts). Secondly, within the mTBI patient group, the relation between DTI measures of damaged tracts and impaired mathematical skills were assessed using Spearman's partial correlation ($p < .05$, two tailed) which were controlled for age, sex and verbal ability. Partial eta-squared was included as a measure of effect size. An effect size of .02 is considered as small, one of .13 as medium and one of .26 as large.[115]

Results

Participant characteristics

Participants' characteristics for each group are displayed in Table 2. The mTBI group and control group were matched on age, sex and handedness. Both groups were also matched on verbal-ability (i.e. Vocabulary subtest) but not on non-verbal ability (i.e. Block Design subtest), and consequently not on estimated total IQ. However, it should be emphasized that all children had normal intelligence (IQ $\geq$ 85) and that non-verbal ability and estimated IQ of the patient group were both average. Differences between TBI children and controls on non-verbal IQ measures are not uncommon.[116-118]

A Wilcoxon signed-ranks test further revealed that mTBI patients and controls were matched on premorbid mathematical abilities. They all had at least an average percentile rank (pc $\geq$ 40) on the standardized mathematical abilities test administered before participation in this study. Finally, there was no significant between-group difference for motor speed. This suggests that subsequent differences in reaction time on the administered tasks cannot be explained by group differences in motor speed.

Mathematics

The mean reaction time and accuracy on the mathematical tasks, as well as the statistics of the group comparisons on these measures, are displayed in Table 3.

With regard to non-symbolic numerical magnitude processing, there was a main effect of group in accuracy: mTBI patients were less accurate in comparing non-symbolic magnitudes than control children. No effect of group was seen for reaction time. There were no significant group differences in accuracy and reaction time for symbolic numerical magnitude processing.

Between-group differences were observed in subitizing reaction time, showing slower reaction times in the subitizing range on the enumeration task for mTBI patients than for control children. There was no effect for group in the accuracy scores of subitizing. Also no main effect for group was seen in accuracy or reaction time for counting.

With regard to small arithmetic problems, there was no significant group effect in accuracy or reaction time. By contrast, a main effect for group was seen in accuracy for large arithmetic problems: mTBI patients were less accurate in solving large addition problems than control children. No significant group effect in reaction time was seen for large arithmetic problems.

Cognitive measures

The descriptive statistics on the cognitive tests, as well as the statistics related to the between-group comparisons are also displayed in Table 3.

With regard to visuospatial working memory, there was a main effect of group: mTBI patients scored significantly lower on Block Recall tasks than control children. There was no significant group difference for verbal working memory.

To evaluate whether the observed group differences in mathematical abilities (i.e. subitizing, non-symbolic processing and large arithmetic problems) could be explained by differences in visuospatial working memory, we repeated the analysis when visuospatial working memory was additionally controlled for. Interestingly, all main effects of group disappeared (all ps $\geq .153$). This indicates that the mathematical difficulties in the mTBI group might be explained by differences in visuospatial working memory.

DTI measures

Due to technical acquisition problems we had to exclude two patients and their matched controls from the analyses. The final DTI sample consisted of 18 mTBI patients and 18 well-matched control children.

Significant main effects of group were present in the corpus callosum (see Fig. 1). More specifically, there were group differences in MD for the CC genu (F(1,35) = 5.38 p = .027; η^2_p = .144; FDR corrected alpha = .004): the mTBI patients demonstrated decreased MD values relative to the control children. Similarly, a main effect of group was present in the mean RD values of the CC genu (F (1,35) = 5.47; p = .026; η^2_p = .146; FDR corrected alpha = .002, with lower RD values in mTBI patients than in control children. No significant group differences for the FA and AD measures in the CC genu were seen. In the FA values, there was only a trend for a group difference (F(1,35) = 3.45; p = .072; η^2_p = .092; FDR corrected alpha = .008), with higher FA values in mTBI patients than in control children. A significant main effect of group was observed in the FA values of the CC splenium (F(1,35) = 4.48; p = .042; η^2_p = .123; FDR corrected alpha = .006), with mTBI patients having higher FA values than control children. There were no other differences observed in the CC splenium.

There were no group differences in DTI metrics in the long association pathways under investigation, i.e. the SLF and ILF (all ps ≥ .100).

Association between CC white matter and mathematical difficulties in the mTBI group

Spearman's partial correlations, controlled for age, sex and verbal ability were computed in the mTBI group between the observed white matter abnormalities in the CC (i.e. increased FA, decreased MD and decreased RD in the genu and splenium) and the impaired mathematical skills (i.e. non-symbolic magnitude processing, subitizing and large arithmetic problem solving). Only a significant correlation between FA (rho = .571; p = .026; FDR corrected alpha = .005) and RD (rho = .544; p = .036; FDR corrected alpha = .011) values in the corpus callosum splenium and large arithmetic problem solving was observed, in which patients with higher FA/lower RD in the splenium were more accurate in solving large arithmetic problems.

The same set of associations was also investigated in the control group. This data revealed several significant and consistent correlations between DTI variables of the corpus callosum and the mathematical measures. More specifically, higher FA (rho = .506; p = .038), lower MD (rho = -.561; p = .019) and lower RD (rho = .598; p = .011) values in the corpus callosum splenium were associated with better non-symbolic magnitude processing. In addition, higher FA (rho = -.521; p = .032), lower MD (rho = .586; p = .013) and lower RD (rho = .593; p = .012) values in the corpus callosum genu were associated with poorer large arithmetic problem solving. All correlations remained significant after FDR correction for multiple comparisons, except the correlation between splenial FA values and non-symbolic magnitude processing (FDR corrected alpha = .005) and the correlation between genial FA values and large arithmetic problems (FDR corrected alpha = .011).

Discussion

Academic problems are one of the major concerns of children with TBI and their parents after injury.[5] Given the pressing need for research on the outcomes of mTBI,[99, 119] especially with regard to the subacute stage of injury, and the fact that several studies in children with TBI have indicated that mathematical achievement is the most compromised after injury,[2, 6, 9] the present study focused on mathematical skills in subacute pediatric mTBI. More specifically, we aimed to characterize elementary mathematical skills in children with subacute mTBI and investigated how their mathematical skills were related to cognitive factors and white matter abnormalities. The results showed subtle deficits in visuospatial mathematical skills as well as a relationship between these difficulties and callosal white matter damage.

The mTBI group and control group were matched on verbal-ability (i.e. Vocabulary subtest) but they differed in non-verbal ability (i.e. Block Design subtest) and consequently estimated IQ. Although IQ tests were previously thought to be insensitive to mTBI, differences between children with mTBI and controls on intellectual measures have been reported.[120, 121] Our findings are also in line with previous research that showed that scores in the non-verbal area are particularly vulnerable immediately after an injury[118] especially when children's' constructional abilities are measured by block and puzzle tasks.[116, 117]

Analysis of the behavioral data revealed that pediatric mTBI induces subtle impairments in rapid apprehension of small numbers of objects, a phenomenon known as subitizing, and subtle deficits in processing of non-symbolic numerosities. These mathematical subskills are known to rely on visuospatial skills. More specifically, visuospatial skills are needed in subitizing[122, 123] and are involved in representing and manipulating mathematical information in spatial form, such as in non-symbolic comparison.[124] Although mathematical difficulties in children with TBI at the (sub)acute stage of injury have been reported,[2, 6, 7] none of the previous studies investigated differences in elementary numerical processing, such as in subitizing or numerical magnitude processing. Our findings are therefore the first to demonstrate specific deficits in such elementary mathematical skills in pediatric mTBI.

The behavioral data also indicate that children with mTBI performed more poorly on the large but not on the small addition problems. Small arithmetic problems are usually solved by means of fact retrieval from long-term memory, whereas large arithmetic problems are more often solved by slower quantity-based procedural strategies, such as counting or decomposing.[125, 126] Accordingly, our findings suggest that while fact retrieval appears to be preserved after injury, children with mTBI perform more poorly on procedural problem solving, a strategy which generally requires more attentional and visuospatial working memory resources.[127] Our findings are congruent with previous studies in children with TBI showing poorer arithmetical performance at the acute stage of injury.[2, 6, 7] However, none of these previous pediatric TBI studies in mathematics looked at differences between arithmetical strategies. Thus, our study extends earlier research by exploring this difference. In particular, we add new information to previous studies in pediatric TBI by showing strategy specific effects on arithmetic.

The current study showed poorer visuospatial, but comparable verbal, working memory in children with mTBI. Deficits in working memory in pediatric TBI are common[2, 20, 22-25, 128] and have been reported after mTBI.[24, 26-28] Interestingly, Treble and colleagues[25] showed impaired visuospatial, but preserved verbal working memory in children with TBI of varying severity and suggested that TBI has domain-specific effects on working memory, as we observed in the current study. However, only the recent study of Loher and colleagues[28] investigated working memory capacity in children with mTBI immediately after injury, revealing subtle working memory deficits 6 weeks after injury, yet these authors did not investigate differences between visuospatial and verbal working memory. We replicate and extend these findings by showing that subtle visuospatial working memory deficits can be observed 4 weeks after the injury.

Barnes and colleagues[129] argued that academic difficulties of children with TBI may be related to impairments in domain general cognitive abilities, such as attention and memory rather than to specific disabilities in reading or mathematics. Our data fit into this hypothesis by showing that the group differences in mathematical abilities disappeared when we additionally controlled for visuospatial working memory. This might suggest that the observed mathematical difficulties may be a consequence of impairments in visuospatial working memory. This echoes previous findings of Ewing-Cobbs and colleagues,[2] who showed that mathematics achievement in pediatric TBI was predicted by visuospatial skills. In typically developing children as well as in children with mathematical difficulties, visuospatial working memory is highly correlated with mathematical abilities[19, 130-133] and predicts future mathematical development.[134, 135] For example, visuospatial abilities are important in holding and manipulating information in mental and complex calculation.[127, 136]

One of the goals of the current study was also to examine white matter abnormalities in children with mTBI and to verify how these abnormalities were related to their mathematical difficulties. We focused on the corpus callosum, superior longitudinal fasciculus and inferior longitudinal fasciculus, which are often damaged after mTBI and which have also been related to individual differences in mathematics achievement. The current DTI data revealed subtle alterations in DTI metrics, i.e. increased FA and decreased MD and RD, in the corpus callosum of children with mTBI at the subacute stage of recovery. No group differences were found in the SLF and ILF, yet it is important to keep in mind that our modest sample size might have limited statistical power to detect group differences with smaller effect sizes. Our findings are in line with previous DTI studies that showed higher FA and lower diffusivity metrics in different callosal regions, after mTBI in both 14-17-year-old adolescents[38, 78] and adults[65, 75, 76] at the subacute stage of recovery. Our results provide the first evidence that such abnormalities are also observed after subacute mTBI in children of a younger age (7-13 years). It should be noted that the observed group differences in DTI metrics were subtle. Given that the participants were all scanned within 4 weeks after injury, it is plausible that some of the subacute abnormalities may evolve into more chronic white matter changes. Indeed, there is evidence for changes in callosal microstructure over time since injury both in adults[65] and children.[137]

As described in the introduction, the interpretation of group differences in DTI metrics in light of underlying microscopic pathology is particularly challenging.[55, 75] DTI metrics can be highly variable depending on the severity of injury and neuropathology, even within the range of mTBI.[138] It should be noted that subtle cytotoxic edema accompanied with an extracellular to intracellular shift of water that occurs early in the course of injury provide the most plausible explanation of the observed pattern in DTI measures in previous studies[38, 73, 76, 79] as well as the current study. It could be possible that changes in the structure of myelin (i.e. decreases in water content within the myelin sheath rather than in the extracellular space) provides an alternative explanation for the increased FA and decreased RD. However, animal models of mTBI pointed to disruptions to axonal rather than to myelin changes.[82, 139] In addition, recent findings on neural fibers from both animals and humans indicate that axon properties, rather than myelin, play a predominant role in anisotropy.[140-145]

Our DTI results are also consistent with previous adult mTBI studies showing that the corpus callosum is particularly vulnerable to injury both at subacute and chronic stages of recovery.[97] Damage to white matter tracts seems to affect unmyelinated fibers more and worse than myelinated fibers. As the majority of the corpus callosum fibers are unmyelinated, the corpus callosum may be particularly vulnerable to traumatic axonal injury.[146, 147]

We also investigated the relationship between altered DTI metrics in the corpus callosum in children with mTBI and their mathematical difficulties. Overall, these correlations were non-significant and inconsistent. More specifically, only a significant correlation between splenial FA and RD values and large arithmetic problem solving was observed. Patients with higher splenial FA values and lower splenial RD values were more accurate in solving large arithmetic problems. However, in the MD values of the splenium such pattern was not observed. Moreover, the direction of the correlation was the inverse of what one would expect based on the results of the group analyses (i.e. increased FA/decreased RD values together with worse mathematical performance in mTBI patients compared to controls). Our results are therefore in line with previous findings of Mayer and colleagues,[79] who showed no association between altered DTI metrics and the observed neuropsychological deficits in subacute pediatric mTBI.

We also repeated the same correlation analyses in the control group. These data revealed significant and consistent correlations between DTI variables of the corpus callosum and mathematical measures. More specifically, higher FA and lower MD/RD in the corpus callosum genu were associated with better non-symbolic magnitude processing. This observation replicates previous findings in typically developing young children showing an association between non-symbolic comparison and parietal fibers of the corpus callosum.[87] In addition, higher FA and lower MD/RD in the corpus callosum genu were associated with poorer large arithmetic problem solving. This observation is in line with recent findings in children showing that higher FA in frontal projections of the corpus callosum is associated with worse cognitive control skills,[148] which are known to be important in procedural arithmetic problem solving. Under the assumption that the corpus callosum plays an integrative role in hemispheric lateralization, it might be that a higher structural connectivity in weak mathematics achievers (as reflected by a higher FA) coincides with an atypical hemispheric asymmetry. Indeed, weak mathematics achievers might compensate by relying more on bilateral (pre)frontal areas and therefore, there might be a better structural connection in the genu of the corpus callosum. A similar explanation for the inverse association between callosal FA and reading ability has recently been put forward in the domain of dyslexia, where children with poor reading achievement showed higher callosal FA compared to average achievers.[149]

It is important to note that even though all children with mTBI were scanned within 4 weeks of injury, there were differences between mTBI participants in the number of days after injury. These differences might have affected the findings of the current study. We therefore tested whether the number of days post-injury was associated with all behavioral and neural measures that were collected. There were no associations between these latter measures and the number of days since injury. Therefore, our current findings are not affected by the number of days since injury.

The data presented in this report showed mathematical difficulties related to impairments in visuospatial working memory as well as subtle damage in the corpus callosum in children with subacute mTBI. Future longitudinal DTI studies should expand upon these findings by characterizing longitudinal changes in white matter and their relation to mathematical difficulties after pediatric TBI.

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Author Disclosure Statement

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Tables

Table 1. Summary of demographic and injury characteristics for the pediatric mTBI group

mTBI patient number	Age (years)	Gender	Handedness	Mechanism of injury	IQ	Days post-injury (behavioral testing)	Days post-injury (MRI)
1	7.73	F	RH	Fall	100	4	19
2	10.91	M	RH	Traffic	94	15	30
3	10.46	M	RH	Fall/sports	103	18	23
4	11.19	F	RH	Fall/sports	91	16	17
5	9.87	M	RH	Collision/sports	97	4	6
6	12.15	F	LH	Traffic	106	2	7
7	11.80	M	RH	Traffic	94	11	26
8	8.56	M	RH	Fall/sports	117	10	14
9	11.89	F	RH	Fall/sports	88	10	16
10	10.51	M	RH	Collision/sports	97	22	23
11	11.11	M	RH	Fall	115	24	25
12	10.43	F	RH	Collision/sports	109	26	30
13	12.16	M	RH	Unknown	117	9	19
14	13.09	M	RH	Collision	109	26	30
15	7.00	M	LH	Fall	100	9	30
16	10.70	M	RH	Fall/sports	85	11	17
17	10.68	F	LH	Fall/sports	103	8	13
18	12.01	M	RH	Traffic	112	2	14
19	10.79	M	RH	Collision	85	16	21
20	12.90	F	RH	Collision/sports	109	14	25

Table 2. Participant characteristics.

	Pediatric mTBI patients	Controls
N	20	20
Age (years)		
Mean (SD)	10.80 (1.58)	10.88 (1.46)
Range	7.00-13.09	7.55-12.81
Sex, M/F	13/7	13/7
Handedness, R/L	17/3	18/2
IQ	102** (10)	113** (9)
Verbal ability	10.00 (1.75)	11.15 (1.95)
Non-verbal ability	10.56* (3.53)	13.10* (2.59)
Premorbid mathematical abilities (pc)		
Mean (SD)	72.46 (16.44)	78.37 (15.51)
Range	40.00-94.50	45.00-97.00
Motor speed (reaction time, ms)	460.27 (104.64)	453.26 (90.39)

* p <.05; ** p < .01

Table 3. Experimental measures.

		Pediatric mTBI patients	Controls	F	*p*	η^2_p
Mathematical abilities						
Numerical magnitude processing						
Non-symbolic	Accuracy	.85 (.07)	.89 (.07)	5.092	.030[a]	.124
	RT (ms)	949.91 (185.41)	963.51 (182.59)	.166	.686	.005
Symbolic	Accuracy	.97 (.03)	.98 (.01)	3.305	.077	.085
	RT (ms)	641.41 (122.98)	669.75 (128.22)	1.394	.245	.037
Enumeration						
Subitizing	Accuracy	.98 (.04)	.97 (.07)	.365	.549	.010
	RT (ms)	1006.25 (176.59)	884.29 (142.98)	6.114	.018[a]	.145
Counting	Accuracy	.88 (.09)	.89 (.16)	.001	.978	<.001
	RT (ms)	2307.64 (521.89)	2210.86 (585.05)	1.115	.298	.030
Arithmetic						
Small problems	Accuracy	.94 (.07)	.96 (.05)	1.836	.185	.053
	RT (ms)	1598.73 (617.35)	1466.44 (739.14)	<.001	.993	<.001
Large problems	Accuracy	.82 (.15)	.91 (.09)	6.142	.018[a]	.157
	RT (ms)	2307.69 (728.94)	2063.77 (838.08)	.280	.600	.008
Cognitive measures						
Working memory						
Visuospatial		21.40 (4.36)	25.75 (4.15)	12.945	.001[b]	.264
Verbal		18.90 (4.22)	20.65 (4.65)	2.352	.134	.06

[a] FDR corrected alpha = .0125; [b] FDR corrected alpha = .025

Figures

Fig. 1. Mean DTI measures of CC genu and splenium (* $p < .05$). Error bars depict 1SE of the mean.